PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
TERESA A. LAVOIE
FISH & RICHARDSON P.C.
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 253240025WO1	Date of mailing *(day/month/year)* **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 10/30895	International filing date *(day/month/year)* 13 April 2010 (13.04.2010)
Applicant CUREMARK LLC	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 8270

   For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/220 (January 2004) *(See notes on accompanying sheet)*

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
TERESA A. LAVOIE
FISH & RICHARDSON P.C.
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing *(day/month/year)*	09 JUN 2010
Applicant's or agent's file reference 253240025WO1	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 10/30895	International filing date *(day/month/year)* 13 April 2010 (13.04.2010)
Applicant CUREMARK LLC	

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   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 8270

   For more detailed instructions, see the notes on the accompanying sheet.

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3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ *no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.*

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/220 (January 2004) *(See notes on accompanying sheet)*

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 253240025WO1	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 10/30895	International filing date *(day/month/year)* 13 April 2010 (13.04.2010)	(Earliest) Priority Date *(day/month/year)* 13 April 2009 (13.04.2009)
Applicant CUREMARK LLC		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. ***Basis of the report***

   a. With regard to the **language**, the international search was carried out on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ ***Unity of invention is lacking*** (see Box No. III).

4. With regard to the **title**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

   a. the figure of the **drawings** to be published with the abstract is Figure No. 7

   ☐ as suggested by the applicant.

   ☐ as selected by this Authority, because the applicant failed to suggest a figure.

   ☒ as selected by this Authority, because this figure better characterizes the invention.

   b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/30895

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 25/28; A61K 9/127 (2010.01)
USPC - 424/420; 424/450
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC - 424/420; 424/450

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 424/420; 424/450 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB, USPT, USOC, EPAB, JPAB); Google
Search terms used: Digestive, pancreatic, enzyme, encapsulation, encapsulated, encapsulating, emulsifiable, lipid, autism, ADD, ADHD, Parkinson's, cystic fibrosis, neurological condition, food grade emulsifiable lipid, mesh and sachet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2004/0121002 A1 (Lee et al.) 24 June 2004 (24.06.2004), especially para [0013]-[0014], [0016], [0020]-[0022], [0024], [0039]-[0044], [0049], [0056], [0061]-[0064] and [0082]	1-59
Y	US 2008/0279839 A1 (Schuler et al.) 13 November 2008 (13.11.2008), especially para [0006], [0016]-[0017], [0028]-[0030], [0046] and [0048]-[0049]	1-59
Y	US 5,324,514 A (Sipos) 28 June 1994 (28.06.1994), especially col 4, ln 24-27, 47 and 62-63; and col 7, ln 67	3-5, 12, 13, 19-21, 40, 41, 53-59
A	US 2006/0183180 A1 (Fallon) 17 August 2006 (17.08.2006), entire document	1-59

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 May 2010 (25.05.2010)	09 JUN 2010
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: TERESA A. LAVOIE
FISH & RICHARDSON P.C.
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	09 JUN 2010
Applicant's or agent's file reference 253240025WO1	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 10/30895	13 April 2010 (13.04.2010)	13 April 2009 (13.04.2009)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A01N 25/28; A61K 9/127 (2010.01)
USPC - 424/420; 424/450

Applicant CUREMARK LLC

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	25 May 2010 (25.05.2010)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2009)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/30895

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/30895

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; *citations and explanations supporting such statement***

1. Statement

Novelty (N)	Claims	1-59	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-59	NO
Industrial applicability (IA)	Claims	1-59	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1, 2, 6-11, 14-18, 22-39, and 42-52 lack an inventive step under PCT Article 33(3) as being obvious over US 2004/0121002 A1 to Lee et al. (hereinafter "Lee") in view of US 2008/0279839 A1 to Schuler et al. (hereinafter "Schuler")

Regarding claim 1, 2, and 15-17; Lee teaches an encapsulated enzyme preparation (para [0013], teaching "an encapsulated bioactive substance composite", with para [0021], expressly teaching "bioactive substances" to include enzymes) comprising: (a) a core containing an enzyme particle (para [0022], teaching a "core which contains the bioactive substance", with para [0021], expressly teaching "bioactive substances" to include enzymes); and (b) a coating comprising an emulsifiable lipid (para [0022], teaching a "coating" which comprises an "emulsifiable lipid"); wherein the coating continuously coats the core (para [0040], "the bioactive substance core is encapsulated in a continuous coating") and the emulsifiable lipid emulsifies upon exposure to a solvent, (para [0041], teaching wherein the emulsifiable lipid coating is emulsified "when the composites are exposed to a solvent"); and wherein the enzyme is present in the preparation in an amount of from about 5% to 95% by weight of the particles, more specifically about 70% or about 80% (para [0039], teaching a preferred concentration of "bioactive substance" of between 50% and 85% of the "encapsulated composite").
Lee fails to expressly teach wherein the encapsulated enzyme is a pancreatic or digestive enzyme, more specifically an amount of pancreatic or digestive enzymes effective for treating cystic fibrosis. However, Lee does teach the encapsulation of a "bioactive substance" (para [0013]), including yeast (para [0020]) and enzymes (para [0021]). Schuler further teaches compositions which comprise yeast digestive enzymes, such as "lipases from C. cylindracea" (para [0016]) which can be "granulated" and "film-coated" (para [0048]), and thereafter used to treat "pancreatic enzyme insufficiency" and related diseases such as "cystic fibrosis" (para [0028]-[0030]). Furthermore, Schuler teaches the encapsulation of "pancreatic enzyme preparations" within "acid resistant microspheres" as being well known to those with ordinary skill in the art (para [0006]). It would therefore have been obvious to one with ordinary skill in the art to use the yeast-or-enzyme encapsulation preparation taught in Lee to encapsulate yeast digestive enzymes to allow for treatment of pancreatic diseases such as cystic fibrosis.
It would have been obvious to one with ordinary skill in the art to include the components taught in Schuler within the preparations taught in Lee because Lee expressly teaches preparations for the encapsulation of yeast and enzymes, and Schuler teaches specific yeast digestive enzymes which can be used to effectively treat certain disease; such that incorporation of the components in Schuler improve the effectiveness and marketability of the encapsulated enzyme preparations.

Regarding claim 10; Lee teaches pharmaceutical composition comprising a therapeutically effective amount of an encapsulated enzyme preparation (para [0013], teaching "an encapsulated bioactive substance composite", with para [0021], expressly teaching "bioactive substances" to include enzymes), comprising a core which comprises an amount of enzyme (para [0022], teaching a "core which contains the bioactive substance", with para [0021], expressly teaching "bioactive substances" to include enzymes); and a coating comprising an emulsifiable lipid (para [0022], teaching a "coating" which comprises an "emulsifiable lipid").
Lee fails to expressly teach wherein the encapsulated enzyme is a pancreatic or digestive enzyme effective for treating cystic fibrosis. However, Lee does teach the encapsulation of a "bioactive substance" (para [0013]), including yeast (para [0020]) and enzymes (para [0021]). Schuler further teaches compositions which comprise yeast digestive enzymes, such as "lipases from C. cylindracea" (para [0016]) which can be "granulated" and "film-coated" (para [0048]), and thereafter used to treat "pancreatic enzyme insufficiency" and related diseases such as "cystic fibrosis" (para [0028]-[0030]). Furthermore, Schuler teaches the encapsulation of "pancreatic enzyme preparations" within "acid resistant microspheres" as being well known to those with ordinary skill in the art (para [0006]). It would therefore have been obvious to one with ordinary skill in the art to use the yeast-or-enzyme encapsulation preparation taught in Lee to encapsulate yeast digestive enzymes to allow for treatment of pancreatic diseases such as cystic fibrosis.
It would have been obvious to one with ordinary skill in the art to include the components taught in Schuler within the preparations taught in Lee because Lee expressly teaches preparations for the encapsulation of yeast and enzymes, and Schuler teaches specific yeast digestive enzymes which can be used to effectively treat certain disease; such that incorporation of the components in Schuler improve the effectiveness and marketability of the encapsulated enzyme preparations.

Regarding claim 6; claim 1 is obvious as above. Furthermore, Lee teaches wherein the lipid is hydrogenated soy oil (para [0044], teaching wherein "the emulsifiable lipid can be derived from... soybean oil," and also teaching wherein "the lipid is preferably hydrogenated").

-- Please See Supplemental Box 1 --

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/30895

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box V.2. Citations and explanations:

Regarding claim 7 and 34; claim 1 and claim 10 is obvious as above. Lee and Schuler fail to expressly teach wherein at least about 80% of the enzyme is released by 30 minutes in a dissolution test performed at pH 6.0. However, Lee does teach that the "rate of release" of the bioactive substance is dependent on several factors, including monoglyceride concentrations (para [0061]), lipid additive concentrations (para [0056]), the nature of the encapsulated bioactive substance (para [0064]), environmental conditions such as mixing shear (para [0064]), and the nature and concentration of emulsifying solvent (para [0064]). Routine experimentation would therefore have shown the optimization of physical parameters which control the rate of release so to produce a preparation having at least about 80% of the enzyme released by 30 minutes in a dissolution test performed at pH 6.0 to be obvious to one with ordinary skill in the art.

Regarding claims 8 and 9; claim 1 is obvious as above. Furthermore, Lee teaches wherein the coating comprises monoglycerides, more specifically wherein the coating consists essentially of one or more monoglycerides (para [0016], "a coating which consists essentially of one or more monoglycerides").

Regarding claim 11; claim 10 is obvious as above. Furthermore, Schuler teaches wherein the composition is in the form of a capsule, a tablet, a pellet, a sachet, or a powder (para [0046], "dosage forms may include, for example, powders, pellets or microspheres, which may optionally be filled into capsules or sachets or be compressed to form tablets").

Regarding claim 14; claim 1 is obvious as above. Furthermore, Lee teaches wherein the emulsifiable lipid is present at about 5%, 30% or 50% by weight in the encapsulated enzyme preparation (para [0063], teaching "emulsifiable lipid" concentrations ranging from 1% to 60%).

Regarding claim 18; claim 1 is obvious as above. Furthermore, Lee teaches wherein the amount of enzyme present in the encapsulated composite is about 70% to 90 % by weight of the encapsulated enzyme preparation (para [0039], teaching a preferred concentration of "bioactive substance" of between 50% and 85% of the "encapsulated composite"), and the emulsifiable lipid is hydrogenated soy oil (para [0044], teaching wherein "the emulsifiable lipid can be derived from... soybean oil," and also teaching wherein "the lipid is preferably hydrogenated").

Regarding claim 22; claim 1 is obvious as above. Furthermore, Lee teaches wherein the emulsifiable lipid comprises at least one hydrophilic group and at least one hydrophobic group (para [0043], "emulsifiable lipids as used herein means those lipids which contain at least one hydrophilic group and at least one hydrophobic group").

Regarding claim 23; claim 22 is obvious as above. Furthermore, Lee teaches wherein the lipid is capable of forming a hydrophilic and hydrophobic interface (para [0043], teaching wherein the "emulsifiable lipids... contain at least one hydrophilic group and at least one hydrophobic group," and also teaching wherein "these chemical and/or physical properties... permit emulsification" into interfaces).

Regarding claims 24 and 25; claim 23 is obvious as above. Furthermore, Lee teaches wherein the interface is a micelle interface or a bilayer interface (para [0043], "interfaces include, for example, micelles and bilayers").

Regarding claim 26; claim 22 is obvious as above. Furthermore, Lee teaches wherein the emulsifiable lipid is derived from animal or vegetable origins (para [0044], "The emulsifiable lipid can be derived from animal or vegetable origins").

Regarding claim 27; claim 26 is obvious as above. Furthermore, Lee teaches wherein the lipid is hydrogenated soy oil (para [0044], teaching wherein "the emulsifiable lipid can be derived from... soybean oil," and also teaching wherein "the lipid is preferably hydrogenated").

Regarding claims 28 and 29; claim 1 is obvious as above. Furthermore, Lee teaches wherein the emulsifiable lipid is hydrogenated, more specifically wherein the emulsifiable lipid consists essentially of hydrogenated soy oil (para [0044], teaching wherein "the emulsifiable lipid can be derived from... soybean oil," and also teaching wherein "the lipid is preferably hydrogenated").

Regarding claim 30; claim 1 is obvious as above. Furthermore, Lee teaches whereinthe emulsifiable lipid is selected from the group consisting of mono glycerides , diglycerides, fatty acids, esters of fatty acids, phospholipids, salts thereof, and combinations thereof (para [0044], "Examples of emulsifiable lipids include, but are not limited to, monoglycerides, diglycerides, fatty acids, esters of fatty acids, phospholipids, salts thereof, and combinations thereof").

Regarding claim 31; claim 1 is obvious as above. Furthermore, Lee teaches wherein the emulsifiable lipid is a food grade emulsifiable lipid (para [0049], "The emulsifiable lipid is preferably a food grade emulsifiable lipid").

Regarding claim 32; claim 31 is obvious as above. Furthermore, Lee teaches wherein the food grade emulsifiable lipid comprises from sorbitan monostearates, sorbitan tristearates, calcium stearoyllactylates, or calcium stearoyllactylates (para [0049], "food grade emulsifiable lipids include sorbitan monostearates, sorbitan tristearates, calcium stearoyl lactylates, and calcium stearoyl lactylates").

Regarding claim 33; claim 22 is obvious as above. Furthermore, Lee teaches wherein the fatty acid esters are selected from the group consisting of acetic acid esters of mono- and diglycerides, citric acid esters of mono- and di-glycerides, lactic acid esters of mono- and di-gylcerides, polyglycerol esters of fatty acids, propylene glycol esters of fatty acids, and diacetyl tartaric acid esters of mono- and diglycerides (para [0049], "Examples of food grade fatty acid esters which are emulsifiable lipids include acetic acid esters of mono- and diglycerides, citric acid esters of mono- and di-glycerides, lactic acid esters of mono- and di-gylcerides, polyglycerol esters of fatty acids, propylene glycol esters of fatty acids, and diacetyl tartaric acid esters of mono- and diglycerides).

-- Please See Supplemental Box 2 --

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/30895

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Supplemental Box 1

Regarding claim 35; claim 1 is obvious as above. Furthermore, Lee teaches wherein the cores are processed by encapsulation (para [0082], teaching the use of "an encapsulation process" to coat a core of bioreactive substance with an emulsifiable lipid coating).

Regarding claim 36; Lee teaches a method for controlling rate of release of an enzyme from an encapsulated enzyme preparation upon exposure to a solvent (para [0024], "a method of controlling the rate of release of a bioactive substance from an encapsulated composite upon exposure to a solvent," with with para [0021], teaching "bioactive substances" to include enzymes), the method comprising: (a) providing enzyme particles (para [0022], teaching a "core which contains the bioactive substance", with para [0021], expressly teaching "bioactive substances" to include enzymes); and (b) coating the enzyme particles with an emulsifiable lipid (para [0022], teaching a "coating" which comprises an "emulsifiable lipid") to form an encapsulated enzyme preparation (para [0040], "the bioactive substance core is encapsulated in a continuous coating").
Lee fails to expressly teach wherein the encapsulated enzyme is a digestive enzyme. However, Lee does teach the encapsulation of a "bioactive substance" (para [0013]), including yeast (para [0020]) and enzymes (para [0021]). Schuler further teaches compositions which comprise yeast digestive enzymes, such as "lipases from C. cylindracea" (para [0016]) which can be "granulated" and "film-coated" (para [0048]), and thereafter used to treat "pancreatic enzyme insufficiency" and related diseases such as "cystic fibrosis" (para [0028]-[0030]). Furthermore, Schuler teaches the encapsulation of "pancreatic enzyme preparations" within "acid resistant microspheres" as being well known to those with ordinary skill in the art (para [0006]). It would therefore have been obvious to one with ordinary skill in the art to use the yeast-or-enzyme encapsulation preparation taught in Lee to encapsulate yeast digestive enzymes to allow for treatment of pancreatic diseases such as cystic fibrosis.
Lee also fails to expressly teach wherein at least about 80% of the enzyme is released by 30 minutes in a dissolution test performed at pH 6.0. However, Lee does teach that the "rate of release" of the bioactive substance is dependent on several factors, including monoglyceride concentrations (para [0061]), lipid additive concentrations (para [0056]), the nature of the encapsulated bioactive substance (para [0064]), environmental conditions such as mixing shear (para [0064]), and the nature and concentration of emulsifying solvent (para [0064]). Routine experimentation would therefore have shown the optimization of physical parameters which control the rate of release so to produce a preparation having at least about 80% of the enzyme released by 30 minutes in a dissolution test performed at pH 6.0 to be obvious to one with ordinary skill in the art.
It would have been obvious to one with ordinary skill in the art to include the components taught in Schuler within the preparations taught in Lee because Lee expressly teaches preparations for the encapsulation of yeast and enzymes, and Schuler teaches specific yeast digestive enzymes which can be used to effectively treat certain disease; such that incorporation of the components in Schuler improve the effectiveness and marketability of the encapsulated enzyme preparations.

Regarding claim 37; Lee teaches a method for controlling rate of release of an enzyme from an encapsulated enzyme preparation upon exposure to a solvent (para [0024], "a method of controlling the rate of release of a bioactive substance from an encapsulated composite upon exposure to a solvent," with with para [0021], teaching "bioactive substances" to include enzymes), the method comprising: (a) providing enzyme particles (para [0022], teaching a "core which contains the bioactive substance", with para [0021], expressly teaching "bioactive substances" to include enzymes); and (b) blending an emulsifiable lipid with an amount of one or more additives to obtain a lipid blend (para [0022], "blending an emulsifiable lipid with an amount of one or more additives to obtain a blend"); and (c) coating the enzyme particles with the lipid blend to form an encapsulated enzyme preparation (para [0022], "coating the bioactive substance with the blend to form an encapsulated bioactive substance"); wherein the emulsifiable lipid and additive are not the same (para [0022], "the emulsifiable lipid and additive are not the same"), and wherein the rate of release of the digestive enzyme from the encapsulated composite is decreased as the amount of additive is increased (para [0022], "the rate of release of the bioactive substance from the encapsulated composite upon exposure to a solvent is decreased as the amount of additive is increased").
Lee fails to expressly teach wherein the encapsulated enzyme is a digestive enzyme. However, Lee does teach the encapsulation of a "bioactive substance" (para [0013]), including yeast (para [0020]) and enzymes (para [0021]). Schuler further teaches compositions which comprise yeast digestive enzymes, such as "lipases from C. cylindracea" (para [0016]) which can be "granulated" and "film-coated" (para [0048]), and thereafter used to treat "pancreatic enzyme insufficiency" and related diseases such as "cystic fibrosis" (para [0028]-[0030]). Furthermore, Schuler teaches the encapsulation of "pancreatic enzyme preparations" within "acid resistant microspheres" as being well known to those with ordinary skill in the art (para [0006]). It would therefore have been obvious to one with ordinary skill in the art to use the yeast-or-enzyme encapsulation preparation taught in Lee to encapsulate yeast digestive enzymes to allow for treatment of pancreatic diseases such as cystic fibrosis.
It would have been obvious to one with ordinary skill in the art to include the components taught in Schuler within the preparations taught in Lee because Lee expressly teaches preparations for the encapsulation of yeast and enzymes, and Schuler teaches specific yeast digestive enzymes which can be used to effectively treat certain disease; such that incorporation of the components in Schuler improve the effectiveness and marketability of the encapsulated enzyme preparations.

-- Please see Supplemental Box 3 -

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Supplemental Box 2

Regarding claim 38; Lee teaches a method for controlling rate of release of an enzyme from an encapsulated composite upon exposure to a solvent (para [0024], "a method of controlling the rate of release of a bioactive substance from an encapsulated composite upon exposure to a solvent," with with para [0021], teaching "bioactive substances" to include enzymes), the method comprising: (a) providing enzyme particles (para [0022], teaching a "core which contains the bioactive substance", with para [0021], expressly teaching "bioactive substances" to include enzymes); and (b) blending an emulsifiable lipid with an amount of one or more additives to obtain a lipid blend (para [0022], "blending an emulsifiable lipid with an amount of one or more additives to obtain a blend"); and (c) coating the enzyme particles with the lipid blend to form an encapsulated enzyme preparation (para [0022], "coating the bioactive substance with the blend to form an encapsulated bioactive substance"); wherein the emulsifiable lipid and additive are not the same (para [0022], "the emulsifiable lipid and additive are not the same"), and wherein the rate of release of the digestive enzyme from the encapsulated composite is decreased as the amount of additive is increased (para [0022], "the rate of release of the bioactive substance from the encapsulated composite upon exposure to a solvent is decreased as the amount of additive is increased").
Lee fails to expressly teach wherein the encapsulated enzyme is a digestive enzyme. However, Lee does teach the encapsulation of a "bioactive substance" (para [0013]), including yeast (para [0020]) and enzymes (para [0021]). Schuler further teaches compositions which comprise yeast digestive enzymes, such as "lipases from C. cylindracea" (para [0016]) which can be "granulated" and "film-coated" (para [0048]), and thereafter used to treat "pancreatic enzyme insufficiency" and related diseases such as "cystic fibrosis" (para [0028]-[0030]). Furthermore, Schuler teaches the encapsulation of "pancreatic enzyme preparations" within "acid resistant microspheres" as being well known to those with ordinary skill in the art (para [0006]). It would therefore have been obvious to one with ordinary skill in the art to use the yeast-or-enzyme encapsulation preparation taught in Lee to encapsulate yeast digestive enzymes to allow for treatment of pancreatic diseases such as cystic fibrosis.
It would have been obvious to one with ordinary skill in the art to include the components taught in Schuler within the preparations taught in Lee because Lee expressly teaches preparations for the encapsulation of yeast and enzymes, and Schuler teaches specific yeast digestive enzymes which can be used to effectively treat certain disease; such that incorporation of the components in Schuler improve the effectiveness and marketability of the encapsulated enzyme preparations.

Regarding claim 39; claim 38 is obvious as above. Furthermore, Lee teaches wherein the emulsifiable lipid is hydrogenated soy oil (para [0044], teaching wherein "the emulsifiable lipid can be derived from... soybean oil," and also teaching wherein "the lipid is preferably hydrogenated").

Regarding claim 42; Schuler teaches a method of treatment (para [0017], "method of treating patients with pancreatic insufficiency") comprising administering to a subject with cystic fibrosis (para [0028]-[0030], teaching an enzyme composition which can be used to treat "pancreatic enzyme insufficiency" and related diseases such as "cystic fibrosis") at least two doses of a composition (para [0017], "one or more of the enzymes are administered separately") comprising a therapeutically effective amount of an encapsulated digestive enzyme preparation (para [0017], "administering a digestive enzyme composition according to this invention", with para [0048], teaching wherein the enzyme can be "granulated" and "film-coated," and with para [0006], teaching the encapsulation of "pancreatic enzyme preparations" within "acid resistant microspheres" as being well known to those with ordinary skill in the art).
Schuler fails to teach the further claim limitation taught by Lee, namely wherein the encapsulated digestive enzyme preparation comprises: (a) a core comprising the enzyme (para [0022], teaching a "core which contains the bioactive substance", with para [0021], expressly teaching "bioactive substances" to include enzymes); and (b) a coating comprising an emulsifiable lipid (para [0022], teaching a "coating" which comprises an "emulsifiable lipid").
It would have been obvious to one with ordinary skill in the art to include the components taught in Lee within the method taught in Schuler because Schuler expressly teaches the use of coated yeast digestive enzymes in pharmacuetical treatment methods, and Lee teaches specific methods for effectively coating and encapsulating yeast and enzymes for oral consumption; wherein incorporation of the components in Lee improve the effectiveness and marketability of the treatment methods and related encapsulated enzyme products.

Regarding claim 43; Schuler teaches a method of administering digestive enzymes to a subject with cystic fibrosis (para [0028]-[0030], teaching a digestive enzyme composition which can be used to treat "pancreatic enzyme insufficiency" and related diseases such as "cystic fibrosis"), comprising administering at least two doses (para [0017], "one or more of the enzymes are administered separately") of an encapsulated enzyme preparation (para [0017], "administering a digestive enzyme composition according to this invention", with para [0048], teaching wherein the enzyme can be "granulated" and "film-coated," and with para [0006], teaching the encapsulation of "pancreatic enzyme preparations" within "acid resistant microspheres" as being well known to those with ordinary skill in the art).
Lee and Schuler fail to expressly teach wherein at least about 80% of the enzyme is released by 30 minutes in a dissolution test performed at pH 6.0. However, Lee does teach that the "rate of release" of the bioactive substance is dependent on several factors, including monoglyceride concentrations (para [0061]), lipid additive concentrations (para [0056]), the nature of the encapsulated bioactive substance (para [0064]), environmental conditions such as mixing shear (para [0064]), and the nature and concentration of emulsifying solvent (para [0064]). Routine experimentation would therefore have shown the optimization of physical parameters which control the rate of release so to produce a preparation having at least about 80% of the enzyme released by 30 minutes in a dissolution test performed at pH 6.0 to be obvious to one with ordinary skill in the art.
It would have been obvious to one with ordinary skill in the art to include the components taught in Lee within the method taught in Schuler because Schuler expressly teaches the use of coated yeast digestive enzymes in pharmacuetical treatment methods, and Lee teaches specific methods for effectively coating and encapsulating yeast and enzymes for oral consumption; wherein incorporation of the components in Lee improve the effectiveness and marketability of the administration methods and related encapsulated enzyme sachet products.

-- Please see Supplemental Box 4 --

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Supplemental Box 3

Regarding claim 44; Schuler teaches a method of administering a sachet (para [0046], "dosage forms may include... sachets") comprising an digestive enzyme preparation to a patient in need thereof (para [0017], "administering a digestive enzyme composition according to this invention"), the method comprising providing a powdered preparation (para [0046], "dosage forms may include... powders) housed in a sachet (para [0046], "filled into... sachets") wherein the preparation is administered by addition to food (para [0049], "preferably administered to a patient substantially contemporaneously with food"), through direct administration into the oral cavity (para [0049], teaching wherein the composition is "ingested" with food).
Schuler fails to expressly teach wherein the digestive enzyme preparation comprises an encapsulated digestive enzyme. However, Schuler does teach wherein the digestive enzymes can be "granulated" and "film-coated" (para [0048]), and also teaches the encapsulation of "pancreatic enzyme preparations" within "acid resistant microspheres" as being well known to those with ordinary skill in the art (para [0006]). Furthermore, Lee teaches the encapsulation of a "bioactive substance composite" to allow for controlled release after oral ingestion (para [0022]), with Lee also expressly teaching "bioactive substances" to include enzymes (para [0021]). It would therefore have been obvious to one with ordinary skill in the art to use encapsulated digestive enzymes within the digestive enzyme preparation.
It would have been obvious to one with ordinary skill in the art to include the components taught in Lee within the method taught in Schuler because Schuler expressly teaches the use of coated yeast digestive enzymes in pharmacuetical treatment methods, and Lee teaches specific methods for effectively coating and encapsulating yeast and enzymes for oral consumption; wherein incorporation of the components in Lee improve the effectiveness and marketability of the administration methods and related encapsulated enzyme sachet products.

Regarding claim 45; claim 42 is obvious as above. Furthermore, Lee teaches wherein the encapsulated digestive enzyme preparation contains only one excipient , whereby the safety of administration is increased (para [0014], teaching the use "an emulsifiable lipid," wherein routine experimentation by one with ordinary skill in the art would have shown the use of a single emulsifiable lipid to increase safety of administration).

Regarding claim 46; claim 45 is obvious as above. Furthermore, Lee teaches wherein the excipient is hydrogenated soy oil (para [0044], teaching wherein "the emulsifiable lipid can be derived from... soybean oil," and also teaching wherein "the lipid is preferably hydrogenated").

Regarding claim 47; claim 45 is obvious as above. Schuler and Lee fail to expressly teach wherein the encapsulated digestive enzyme preparation is hypoallergenic. However, Lee does teach a method for encapsulating enzymes which requires no solvents, extenders or excessive excipients (para [0022]), thereby reducing exposure of the preparation to potential allergenic materials. Routine experimentation by one with ordinary skill in the art would therefore have shown encapsulated digestive enzyme preparations produced by the methods taught in Schuler and Lee to by hypoallergenic.

Regarding claim 48; claim 44 is obvious as above. Furthermore, Schuler teaches wherein the individual is susceptible to treatment with digestive enzymes has an enzyme deficiency (para [0028]-[0030], teaching wherein the yeast digestive enzyme compositions cane be used to treat "pancreatic enzyme insufficiency" and related diseases such as "cystic fibrosis").

Regarding claims 49, 50, 51, and 52; claim 48 is obvious as above. Schuler and Lee fail to expressly teach wherein the determination of whether the individual has an enzyme deficiency is made using a pathogenic or biochemical marker, more specifically wherein the marker is FCT level or MET gene mutation. However, the use of pathogenic or biochemical markers, such as FCT levels or MET gene mutations, in diagnosing enzyme deficiencies and related diseases was well known to those with ordinary skill in the art at the time of the invention; such that routine experimentation would have shown the incorporation of steps utilizing diagnostic markers to be important in optimizing the effectiveness, efficiency, safety, and marketability of the sachet administration method, wherein the resulting additional steps would have been obvious to one with ordinary skill in the art.

Claims 3-5, 12, 13, 19-21, 40, 41, and 53-59 lack an inventive step under PCT Article 33(3) as being obvious over Lee in view of Schuler and in further view of US 5,324,514 A (Sipos)

Regarding claims 3, 4 and 40; claims 1 and 36 are obvious as above. Neither Lee nor Schuler expressly teaches wherein the core enzyme particles are between about 105 .mu.m/140 mesh and about 425 .mu.m./40 mesh. However, Schuler does teach wherein the compositions can be "granulated" (para [0048]), and thereafter used to treat "pancreatic enzyme insufficiency" and related diseases such as "cystic fibrosis" (para [0028]-[0030]). Sipos further teaches a "digestive enzyme" composition which is "microencapsulated" (col 4, ln 62-63) and which can thereafter be used to treat pancreatic diseases such as "cystic fibrosis" (col 4, ln 47). Sipos also expressly teaches the formation of "80 mesh particles" (col 7, ln 67) and further teaches that 80 mesh microspheres "are especially beneficial for use to treat pancreatic enzymes... deficiencies in cystic fibrosis children" (col 4, ln 24-27). It would therefore have been obvious to one with ordinary skill in the art to optimize the particles size of the encapsulated enzymes to a #80 mesh, equivalent to 177 microns, such that the resulting core enzyme particles would be between about 105 .mu.m/140 mesh and about 425 .mu.m./40 mesh.
It would have been obvious to one with ordinary skill in the art to include the components taught in Sipos within the preparation taught in Lee and Schuler because Lee and Schuler combine to teach encapsulated digestive enzymes which can be used to effectively treat cystic fibrosis in a patient; and Sipos adds specificity to particular parameters of encapsulated digestive enzymes such as optimal core-particle size, which thereby improves the effectiveness, efficiency, stability, and marketability of the encapsulated enzyme preparation and related products.

-- Please see Supplemental Box 5 --

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
Supplemental Box 4

Regarding claim 5; claim 1 is obvious as above. Neither Lee nor Schuler expressly teaches wherein the preparation is non-aerosolizable. However, Schuler does teach wherein the compositions can be "granulated" (para [0048]), and thereafter used to treat "pancreatic enzyme insufficiency" and related diseases such as "cystic fibrosis" (para [0028]-[0030]). Sipos further teaches a "digestive enzyme" composition which is "microencapsulated" (col 4, ln 62-63) and which can thereafter be used to treat pancreatic diseases such as "cystic fibrosis" (col 4, ln 47). Sipos also expressly teaches the formation of "80 mesh particles" (col 7, ln 67) and further teaches that 80 mesh microspheres "are especially beneficial for use to treat pancreatic enzymes... deficiencies in cystic fibrosis children" (col 4, ln 24-27). One with ordinary skill in the art at the time of the invention would have known the term "non-aerosolizable" to indicate an encapsulated enzyme preparation where less than about 15% of the particles can be sieved through #100 mesh/150 micron; such that routine experimentation would have shown the optimization of encapsulated-enzyme particle size to #80 mesh/177micron particles to result in a non-aerosolizable preparation.
It would have been obvious to one with ordinary skill in the art to include the components taught in Sipos within the preparation taught in Lee and Schuler because Lee and Schuler combine to teach encapsulated digestive enzymes which can be used to effectively treat cystic fibrosis in a patient; and Sipos adds specificity to particular parameters of encapsulated digestive enzymes such as optimal core-particle size, which thereby improves the effectiveness, efficiency, stability, and marketability of the encapsulated enzyme preparation and related products.

Regarding claims 12 and 13; Lee teaches an enzyme delivery system comprising encapsulated enzyme preparation (para [0013], teaching "an encapsulated bioactive substance composite", with para [0021], expressly teaching "bioactive substances" to include enzymes) having particles which comprise: a core comprising enzymes (para [0022], teaching a "core which contains the bioactive substance", with para [0021], expressly teaching "bioactive substances" to include enzymes) present in an amount of from about 5% to 95% by weight of the particles (para [0039], teaching a preferred concentration of "bioactive substance" of between 50% and 85% of the "encapsulated composite"); and a generally uniform coating (para [0040], "the bioactive substance core is encapsulated in a continuous coating") to provide for controlled release of the enzymes (para [0024], "the coating... allows for controlled release of the bioactive substance"), said coating comprising an emulsifiable lipid (para [0022], teaching a "coating" which comprises an "emulsifiable lipid").
Lee fails to expressly teach wherein the encapsulated enzyme is a pancreatic or digestive enzyme, more specifically an amount of pancreatic or digestive enzymes effective for treating cystic fibrosis. However, Lee does teach the encapsulation of a "bioactive substance" (para [0013]), including yeast (para [0020]) and enzymes (para [0021]). Schuler further teaches compositions which comprise yeast digestive enzymes, such as "lipases from C. cylindracea" (para [0016]) which can be "granulated" and "film-coated" (para [0048]), and thereafter used to treat "pancreatic enzyme insufficiency" and related diseases such as "cystic fibrosis" (para [0028]-[0030]). Furthermore, Schuler teaches the encapsulation of "pancreatic enzyme preparations" within "acid resistant microspheres" as being well known to those with ordinary skill in the art (para [0006]). It would therefore have been obvious to one with ordinary skill in the art to use the yeast-or-enzyme encapsulation preparation taught in Lee to encapsulate yeast digestive enzymes to allow for treatment of pancreatic diseases such as cystic fibrosis.
Lee and Schuler fail to expressly teach wherein the preparation particles are non-aerosolizable. However, Schuler does teach wherein the compositions can be "granulated" (para [0048]), and thereafter used to treat "pancreatic enzyme insufficiency" and related diseases such as "cystic fibrosis" (para [0028]-[0030]). Sipos further teaches a "digestive enzyme" composition which is "microencapsulated" (col 4, ln 62-63) and which can thereafter be used to treat pancreatic diseases such as "cystic fibrosis" (col 4, ln 47). Sipos also expressly teaches the formation of "80 mesh particles" (col 7, ln 67) and further teaches that 80 mesh microspheres "are especially beneficial for use to treat pancreatic enzymes... deficiencies in cystic fibrosis children" (col 4, ln 24-27). One with ordinary skill in the art at the time of the invention would have known the term "non-aerosolizable" to indicate an encapsulated enzyme preparation where less than about 15% of the particles can be sieved through #100 mesh/150 micron; such that routine experimentation would have shown the optimization of encapsulated-enzyme particle size to #80 mesh/177micron particles to result in a non-aerosolizable preparation.
It would have been obvious to one with ordinary skill in the art to include the components taught in Schuler within the preparations taught in Lee because Lee expressly teaches preparations for the encapsulation of yeast and enzymes, and Schuler teaches specific yeast digestive enzymes which can be used to effectively treat certain disease; such that incorporation of the components in Schuler improve the effectiveness and marketability of the encapsulated enzyme preparations.
It would have been obvious to one with ordinary skill in the art to include the components taught in Sipos within the preparation taught in Lee and Schuler because Lee and Schuler combine to teach encapsulated digestive enzymes which can be used to effectively treat cystic fibrosis in a patient; and Sipos adds specificity to particular parameters of encapsulated digestive enzymes such as optimal core-particle size, which thereby improves the effectiveness, efficiency, stability, and marketability of the encapsulated enzyme preparation and related products.

-- Please See Supplemental Box 6 --

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Supplemental Box 5

Regarding claims 19 and 20; claim 1 is obvious as above. Neither Lee nor Schuler expressly teaches wherein the encapsulated enzyme preparation contains particles, and further wherein at least about 75% of the particles are between about #40 and #80 mesh, or about 180 to 425 .mu.m, and also wherein less than about 15% of the encapsulated enzyme preparation particles can be sieved through #100 mesh, or about 150 .mu.m. However, Schuler does teach wherein the compositions can be "granulated" (para [0048]), and thereafter used to treat "pancreatic enzyme insufficiency" and related diseases such as "cystic fibrosis" (para [0028]-[0030]). Sipos further teaches a "digestive enzyme" composition which is "microencapsulated" (col 4, ln 62-63) and which can thereafter be used to treat pancreatic diseases such as "cystic fibrosis" (col 4, ln 47). Sipos also expressly teaches the formation of "80 mesh particles" (col 7, ln 67) and further teaches that 80 mesh microspheres "are especially beneficial for use to treat pancreatic enzymes... deficiencies in cystic fibrosis children" (col 4, ln 24-27). It would therefore have been obvious to one with ordinary skill in the art to optimize the particles size of the encapsulated enzymes to a #80 mesh, equivalent to 177 microns, such that at least about 75% of the particles are between about #40 and #80 mesh, or about 180 to 425 .mu.m, and also wherein less than about 15% of the encapsulated enzyme preparation particles can be sieved through #100 mesh, or about 150 .mu.m.
It would have been obvious to one with ordinary skill in the art to include the components taught in Sipos within the preparation taught in Lee and Schuler because Lee and Schuler combine to teach encapsulated digestive enzymes which can be used to effectively treat cystic fibrosis in a patient; and Sipos adds specificity to particular parameters of encapsulated digestive enzymes such as optimal core-particle size, which thereby improves the effectiveness, efficiency, stability, and marketability of the encapsulated enzyme preparation and related products.

Regarding claim 21; claim 12 is obvious as above. Furthermore, Schuler teaches whereinthe delivery system further comprises a sachet or pouch (para [0046], "dosage forms may include... sachets").

Regarding claim 41; Lee teaches a method for controlling rate of release of an enzyme from an encapsulated enzyme preparation upon exposure to a solvent (para [0024], "a method of controlling the rate of release of a bioactive substance from an encapsulated composite upon exposure to a solvent," with with para [0021], teaching "bioactive substances" to include enzymes), the method comprising: (a) providing enzyme particles (para [0022], teaching a "core which contains the bioactive substance", with para [0021], expressly teaching "bioactive substances" to include enzymes); and (b) coating the enzyme particles with an emulsifiable lipid (para [0022], teaching a "coating" which comprises an "emulsifiable lipid") to form an encapsulated enzyme preparation (para [0040], "the bioactive substance core is encapsulated in a continuous coating").
Lee fails to expressly teach wherein the encapsulated enzyme is a digestive enzyme. However, Lee does teach the encapsulation of a "bioactive substance" (para [0013]), including yeast (para [0020]) and enzymes (para [0021]). Schuler further teaches compositions which comprise yeast digestive enzymes, such as "lipases from C. cylindracea" (para [0016]) which can be "granulated" and "film-coated" (para [0048]), and thereafter used to treat "pancreatic enzyme insufficiency" and related diseases such as "cystic fibrosis" (para [0028]-[0030]). Furthermore, Schuler teaches the encapsulation of "pancreatic enzyme preparations" within "acid resistant microspheres" as being well known to those with ordinary skill in the art (para [0006]). It would therefore have been obvious to one with ordinary skill in the art to use the yeast-or-enzyme encapsulation preparation taught in Lee to encapsulate yeast digestive enzymes to allow for treatment of pancreatic diseases such as cystic fibrosis.
Lee and Schuler fail to expressly teach wherein the encapsulated digestive enzyme preparation consists essentially of particles of less than about 150 .mu.m. However, Schuler does teach wherein the compositions can be "granulated" (para [0048]), and thereafter used to treat "pancreatic enzyme insufficiency" and related diseases such as "cystic fibrosis" (para [0028]-[0030]). Sipos further teaches a "digestive enzyme" composition which is "microencapsulated" (col 4, ln 62-63) and which can thereafter be used to treat pancreatic diseases such as "cystic fibrosis" (col 4, ln 47). Sipos also expressly teaches the formation of particles as small as #80/177 microns (col 7, ln 67) and further teaches that small microspheres "are especially beneficial for use to treat pancreatic enzymes... deficiencies in cystic fibrosis children" (col 4, ln 24-27). Furthermore, routine experimentation by one with ordinary skill in the art would have shown a further reduction of encapsulated enzyme particle size to less than about 150 microns as an effective way of further improving the effectiveness and efficiency of the encapsulated digestive enzymes; such that the use of encapsulated digestive enzyme particles of less than about 150 .mu.m would have been obvious to one with ordinary skill in the art.
It would have been obvious to one with ordinary skill in the art to include the components taught in Schuler within the preparations taught in Lee because Lee expressly teaches preparations for the encapsulation of yeast and enzymes, and Schuler teaches specific yeast digestive enzymes which can be used to effectively treat certain disease; such that incorporation of the components in Schuler improve the effectiveness and marketability of the encapsulated enzyme preparations.
It would have been obvious to one with ordinary skill in the art to include the components taught in Sipos within the method taught in Lee and Schuler because Lee and Schuler combine to teach encapsulated digestive enzymes which can be used to effectively treat cystic fibrosis in a patient; and Sipos adds specificity to particular parameters of encapsulated digestive enzymes such as optimal core-particle size, which thereby improves the effectiveness, efficiency, stability, and marketability of the encapsulated enzyme preparation and related products.

-- Please See Supplemental Box 7 --

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
Supplemental Box 7

Regarding claims 53 and 55; Lee teaches a method of preparing an encapsulated controlled release enzyme preparation with enhanced flow properties, the method comprising: coating enzyme particles (para [0022], teaching a "core which contains the bioactive substance", with para [0021], expressly teaching "bioactive substances" to include enzymes) with an emulsifiable lipid (para [0022], teaching a "coating" which comprises an "emulsifiable lipid") to form an encapsulated enzyme containing a core which contains the enzyme and a coating which contains the emulsifiable lipid (para [0040], "the bioactive substance core is encapsulated in a continuous coating").
Lee fails to expressly teach wherein the encapsulated enzyme is a pancreatic or digestive enzyme effective for treating cystic fibrosis. However, Lee does teach the encapsulation of a "bioactive substance" (para [0013]), including yeast (para [0020]) and enzymes (para [0021]). Schuler further teaches compositions which comprise yeast digestive enzymes, such as "lipases from C. cylindracea" (para [0016]) which can be "granulated" and "film-coated" (para [0048]), and thereafter used to treat "pancreatic enzyme insufficiency" and related diseases such as "cystic fibrosis" (para [0028]-[0030]). Furthermore, Schuler teaches the encapsulation of "pancreatic enzyme preparations" within "acid resistant microspheres" as being well known to those with ordinary skill in the art (para [0006]). It would therefore have been obvious to one with ordinary skill in the art to use the yeast-or-enzyme encapsulation preparation taught in Lee to encapsulate yeast digestive enzymes to allow for treatment of pancreatic diseases such as cystic fibrosis.
Lee and Schuler fail to expressly teach wherein the uncoated enzyme particles are initially screened to obtain particles of a suitable size for encapsulation, more specifically wherein the screened enzyme particles are obtained by sieving digestive enzyme particles using a 40 mesh and a 140 mesh. However, Schuler does teach wherein the compositions can be "granulated" (para [0048]), and thereafter used to treat "pancreatic enzyme insufficiency" and related diseases such as "cystic fibrosis" (para [0028]-[0030]). Sipos further teaches a "digestive enzyme" composition which is "microencapsulated" (col 4, ln 62-63) and which can thereafter be used to treat pancreatic diseases such as "cystic fibrosis" (col 4, ln 47). Sipos also expressly teaches the formation of particles as small as #80 mesh /177 microns (col 7, ln 67), wherein small microspheres "are especially beneficial for use to treat pancreatic enzymes... deficiencies in cystic fibrosis children" (col 4, ln 24-27), and further teaches that "spherical particles if not of uniform size" can be separated "according to desired sizes using U.S. Standard sieve screens" prior to coating the particles (col 6, ln 47-50). It would therefore have been obvious to one with ordinary skill in the art to initially screen the enzyme particles, such as with #40 and #140 screens, so to collect particles which are of an optimal size, such as #80 mesh /177 microns, for encapsulation and subsequent patient treatment.
It would have been obvious to one with ordinary skill in the art to include the components taught in Schuler within the preparations taught in Lee because Lee expressly teaches preparations for the encapsulation of yeast and enzymes, and Schuler teaches specific yeast digestive enzymes which can be used to effectively treat certain disease; such that incorporation of the components in Schuler improve the effectiveness and marketability of the encapsulated enzyme preparations.
It would have been obvious to one with ordinary skill in the art to include the components taught in Sipos within the method taught in Lee and Schuler because Lee and Schuler combine to teach encapsulated digestive enzymes which can be used to effectively treat cystic fibrosis in a patient; and Sipos adds specificity to particular parameters of encapsulated digestive enzymes such as optimal core-particle size, which thereby improves the effectiveness, efficiency, stability, and marketability of the encapsulated enzyme preparation and related products.

Regarding claims 54 and 56; Lee teaches a method of preparing an encapsulated controlled release enzyme preparation, the method comprising: coating enzyme particles (para [0022], teaching a "core which contains the bioactive substance", with para [0021], expressly teaching "bioactive substances" to include enzymes) with an emulsifiable lipid (para [0022], teaching a "coating" which comprises an "emulsifiable lipid") to form an encapsulated enzyme containing a core which contains the enzyme and a coating which contains the blend of emulsifiable lipid (para [0040], "the bioactive substance core is encapsulated in a continuous coating").
Lee fails to expressly teach wherein the encapsulated enzyme is a pancreatic or digestive enzyme effective for treating cystic fibrosis. However, Lee does teach the encapsulation of a "bioactive substance" (para [0013]), including yeast (para [0020]) and enzymes (para [0021]). Schuler further teaches compositions which comprise yeast digestive enzymes, such as "lipases from C. cylindracea" (para [0016]) which can be "granulated" and "film-coated" (para [0048]), and thereafter used to treat "pancreatic enzyme insufficiency" and related diseases such as "cystic fibrosis" (para [0028]-[0030]). Furthermore, Schuler teaches the encapsulation of "pancreatic enzyme preparations" within "acid resistant microspheres" as being well known to those with ordinary skill in the art (para [0006]). It would therefore have been obvious to one with ordinary skill in the art to use the yeast-or-enzyme encapsulation preparation taught in Lee to encapsulate yeast digestive enzymes to allow for treatment of pancreatic diseases such as cystic fibrosis.
Lee and Schuler fail to expressly teach wherein the uncoated enzyme particles are initially screened to obtain digestive enzyme particles ranging from about 105 to 450 microns, more specifically wherein the screened enzyme particles are obtained by sieving digestive enzyme particles using a 40 mesh and a 140 mesh. However, Schuler does teach wherein the compositions can be "granulated" (para [0048]), and thereafter used to treat "pancreatic enzyme insufficiency" and related diseases such as "cystic fibrosis" (para [0028]-[0030]). Sipos further teaches a "digestive enzyme" composition which is "microencapsulated" (col 4, ln 62-63) and which can thereafter be used to treat pancreatic diseases such as "cystic fibrosis" (col 4, ln 47). Sipos also expressly teaches the formation of particles as small as #80 mesh /177 microns (col 7, ln 67), wherein small microspheres "are especially beneficial for use to treat pancreatic enzymes... deficiencies in cystic fibrosis children" (col 4, ln 24-27), and further teaches that "spherical particles if not of uniform size" can be separated "according to desired sizes using U.S. Standard sieve screens" prior to coating the particles (col 6, ln 47-50). It would therefore have been obvious to one with ordinary skill in the art to initially screen the enzyme particles, such as with #40 and #140 screens, so to collect particles which are of an optimal size, such as #80 mesh /177 microns, for encapsulation and subsequent patient treatment.
It would have been obvious to one with ordinary skill in the art to include the components taught in Schuler within the preparations taught in Lee because Lee expressly teaches preparations for the encapsulation of yeast and enzymes, and Schuler teaches specific yeast digestive enzymes which can be used to effectively treat certain disease; such that incorporation of the components in Schuler improve the effectiveness and marketability of the encapsulated enzyme preparations.

**(Please see Supplemental Box 8 for continued analysis of claims 54 and 5

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/30895

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Supplemental Box 7
(Continued analysis of claims 54 and 56 from Supplemental Box 7)

It would have been obvious to one with ordinary skill in the art to include the components taught in Sipos within the method taught in Lee and Schuler because Lee and Schuler combine to teach encapsulated digestive enzymes which can be used to effectively treat cystic fibrosis in a patient; and Sipos adds specificity to particular parameters of encapsulated digestive enzymes such as optimal core-particle size, which thereby improves the effectiveness, efficiency, stability, and marketability of the encapsulated enzyme preparation and related products.

Regarding claim 57; claim 53 is obvious as above. Furthermore, Lee teaches wherein the emulsifiable lipid is hydrogenated soy oil (para [0044], teaching wherein "the emulsifiable lipid can be derived from... soybean oil," and also teaching wherein "the lipid is preferably hydrogenated")

Regarding claims 58 and 59; Lee teaches a method of preparing an encapsulated controlled release enzyme preparation, the method comprising: (a) blending an emulsifiable lipid with an amount of one or more additives to obtain a blend (para [0022], "blending an emulsifiable lipid with an amount of one or more additives to obtain a blend"), (b) coating enzyme particles (para [0022], teaching a "core which contains the bioactive substance", with para [0021], expressly teaching "bioactive substances" to include enzymes) with the lipid blend (para [0022], teaching a "coating" which comprises an "emulsifiable lipid") to form an encapsulated enzyme containing a core which contains the enzyme and a coating which contains the blend of emulsifiable lipid (para [0040], "the bioactive substance core is encapsulated in a continuous coating").
Lee fails to expressly teach wherein the encapsulated enzyme is a pancreatic or digestive enzyme effective for treating cystic fibrosis. However, Lee does teach the encapsulation of a "bioactive substance" (para [0013]), including yeast (para [0020]) and enzymes (para [0021]). Schuler further teaches compositions which comprise yeast digestive enzymes, such as "lipases from C. cylindracea" (para [0016]) which can be "granulated" and "film-coated" (para [0048]), and thereafter used to treat "pancreatic enzyme insufficiency" and related diseases such as "cystic fibrosis" (para [0028]-[0030]). Furthermore, Schuler teaches the encapsulation of "pancreatic enzyme preparations" within "acid resistant microspheres" as being well known to those with ordinary skill in the art (para [0006]). It would therefore have been obvious to one with ordinary skill in the art to use the yeast-or-enzyme encapsulation preparation taught in Lee to encapsulate yeast digestive enzymes to allow for treatment of pancreatic diseases such as cystic fibrosis.
Lee and Schuler fail to expressly teach wherein the uncoated enzyme particles are initially screened to obtain digestive enzyme particles ranging from about 105 to 450 microns. However, Schuler does teach wherein the compositions can be "granulated" (para [0048]), and thereafter used to treat "pancreatic enzyme insufficiency" and related diseases such as "cystic fibrosis" (para [0028]-[0030]). Sipos further teaches a "digestive enzyme" composition which is "microencapsulated" (col 4, ln 62-63) and which can thereafter be used to treat pancreatic diseases such as "cystic fibrosis" (col 4, ln 47). Sipos also expressly teaches the formation of particles as small as #80 mesh /177 microns (col 7, ln 67), wherein small microspheres "are especially beneficial for use to treat pancreatic enzymes... deficiencies in cystic fibrosis children" (col 4, ln 24-27), and further teaches that "spherical particles if not of uniform size" can be separated "according to desired sizes using U.S. Standard sieve screens" prior to coating the particles (col 6, ln 47-50). It would therefore have been obvious to one with ordinary skill in the art to initially screen the enzyme particles so to collect particles which are of an optimal size, such as #80 mesh /177 microns, for encapsulation and subsequent patient treatment.
Lee, Schuler and Sipos fail to epressly teach wherein the method further comprises the step of (d) adjusting batch and oil temperatures during the spray process at periodic time intervals whereby optimal spray conditions are maintained during said process. However, Sipos does teach wherein the encapsulating composition can be sprayed onto the bioactive material core (col 10, ln 15). Furthermore, the use of spray coating as a method of microencapsulation, as well as the related optimization of the spray encapsulation through control and adjustment of ambient conditions such as temperature during the process, was well known to those with ordinary skill in the art at the time of the invention; such that the inclusion of a temperature adjustment step to optimize spray encapsulation would have been obvious to one with ordinary skill in the art.
It would have been obvious to one with ordinary skill in the art to include the components taught in Schuler within the preparations taught in Lee because Lee expressly teaches preparations for the encapsulation of yeast and enzymes, and Schuler teaches specific yeast digestive enzymes which can be used to effectively treat certain disease; such that incorporation of the components in Schuler improve the effectiveness and marketability of the encapsulated enzyme preparations.
It would have been obvious to one with ordinary skill in the art to include the components taught in Sipos within the method taught in Lee and Schuler because Lee and Schuler combine to teach encapsulated digestive enzymes which can be used to effectively treat cystic fibrosis in a patient; and Sipos adds specificity to particular parameters of encapsulated digestive enzymes such as optimal core-particle size, which thereby improves the effectiveness, efficiency, stability, and marketability of the encapsulated enzyme preparation and related products.

Claims 1-59 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used by industry

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*.

In these Notes, "Article," "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Annex B).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, International Phase, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Preliminary Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet or sheets containing a complete set of claims in replacement of all the claims previously filed must be submitted.

Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively in Arabic numerals (Section 205(a)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers: claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"*Statement under Article 19(1)*" *(Rule 46.4)*

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1*bis*(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43*bis*.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, National Chapters.

SEQUENCE LISTINGS AND TABLES RELATED THERETO IN INTERNATIONAL APPLICATIONS FILED IN THE U.S. RECEIVING OFFICE

The Administrative Instructions (AIs) under the Patent Cooperation Treaty (PCT), in force as of **July 1, 2009**, contain important changes relating to the manner of filing, and applicable fees for, sequence listings and/or tables related thereto (sequence-related tables) in international applications. The complete text may be accessed at http://www.wipo.int/pct/en/texts/index.htm.

Effective July 1, 2009, Part 8 and Annex C-*bis* will no longer form part of the AIs. Part 8 was introduced in 2001 as a temporary solution to problems arising from the filing of very large sequence listings on paper and provided for a *sequence listing forming part of the international application* to be filed in electronic form on physical medium (*e.g.*, CD), together with the remainder of the application on paper. In 2002, Part 8 was expanded to include sequence-related tables and Annex C-*bis* was added to provide technical requirements. All applicants may now file complete international applications in electronic form, eliminating the need for these temporary provisions.

I. AIS PART 8 AND ANNEX C-*BIS DELETED AS OF JULY 1, 2009*

A) **Sequence-related tables cannot be filed as a separate part of the description or in text format.** They must be provided as an integral part of the international application either:
- in PDF format as part of an international application filed in electronic form via EFS-Web; or
- on paper as part of an international application filed on paper.

B) **A *sequence listing forming part of an international application*** may be provided either:
- in electronic form, as part of an international application filed in electronic form via EFS-Web, in
  - Annex C/ST.25 text format (preferred), or
  - PDF format; or
- on paper as part of an international application filed on paper.

C) **A *sequence listing not forming part of the international application* (for search under PCT Rule 13*ter*) in Annex C/ST.25 text format**
- is not required where the *sequence listing forming part of the international application* was filed in Annex C/ST.25 text format as part of an international application filed in electronic form via EFS-Web
- is required for search where the *sequence listing forming part of the international application* was filed in PDF
- is required for search on physical medium (*e.g.*, CD) where the *sequence listing forming part of the international application* was filed on paper as part of an international application filed on paper.

II. CALCULATION OF THE INTERNATIONAL FILING FEE AND FEE REDUCTION UNDER AI § 707

A) **A sequence-related table** must form an integral part of the international application and will incur FULL page fees with no upper limit.

B) **A *sequence listing forming part of an international application*** filed:
- via EFS-Web in Annex C/ST.25 text format will incur NO page fees;
- on paper or in PDF format will incur FULL page fees with no upper limit.

III. AVAILABILITY OF SEQUENCE LISTINGS SUBMITTED FOR SEARCH UNDER PCT RULE *13TER*

International Searching Authorities will be required to transmit to the International Bureau a copy of an Annex C/ST.25 text format sequence listing provided for search under PCT Rule 13*ter*. Any such sequence listing will be made available on PATENTSCOPE® (*sequence listings forming part of the international application* are already available).

IV. JULY 2009 REQUEST (PCT/RO/101)

The Request now has two options for the last sheet: one for paper filings; and one for EFS-Web filings. The July 2009 Request may be accessed at http://www.wipo.int/pct/en/forms/index.htm.